Transplant Renal Artery Stenosis

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Abstract. Transplant renal artery stenosis (TRAS) is a recognized, potentially curable cause of posttransplant arterial hypertension, allograft dysfunction, and graft loss. It usually occurs 3 mo to 2 yr after transplantation, but early or later presentations are not uncommon. The prevalence ranges widely from 1 to 23% in different series, reflecting the heterogeneous criteria used to establish the diagnosis, the different manner of preservation of the graft, and surgical expertise. Reported cases are progressively increasing in parallel with the use of non-invasive investigation procedures, such as Doppler ultrasonography and magnetic resonance (MR) angiography, that arouse the suspicion of the disease even in less symptomatic cases. However, definitive diagnosis of hemodynamically significant stenosis rests on the use of invasive angiographic techniques. Percutaneous transluminal angioplasty (PTA) is the treatment of choice and restores kidney perfusion in 60 to 90% of cases. The risk of re-stenosis, the major drawback of the procedure, is prevented by the use of expandable endoprostheses. Surgery is indicated for stenoses that cannot be treated by PTA or that recur after it. Doppler ultrasonography is the procedure of choice to evaluate graft perfusion before and after revascularization.

Complications after Renal Transplantation
For years, the host’s immune response has been the main cause of premature graft loss. In the last two decades, however, calcineurin inhibitors and other powerful immunosuppressive agents have progressively improved immunosuppressive potency and reduced 5-yr graft loss due to acute or chronic rejection to less than 20–30% (1). Thus, the importance of other causes of premature kidney failure such as host death, recurrence of previous disease on the graft, drug toxicity, and vascular complications has progressively risen. In particular, after the 1966 Massachusetts General Hospital report in the New England Journal of Medicine (2), renal artery stenosis of the graft has been more frequently reported and is now recognized as a major cause not only of graft loss, but also of premature death of the host. Prevention, early detection, and effective treatment of renal artery stenosis therefore contribute substantially to graft and patient survival. Recent advances in the understanding and treatment of this condition are the focus of the present review.

Clinical Presentation
Transplant renal artery stenosis (TRAS) is a relatively frequent, potentially curable cause of refractory hypertension and allograft dysfunction that accounts for approximately 1 to 5% of cases of posttransplant hypertension (3) and at least 75% of all posttransplant vascular complications (4). Its incidence varies, depending on the definition and diagnostic techniques used, from 1% to 23% (5). Other determinants of variability of the prevalence are the manner of preservation of the graft (of note, after the introduction of block perfusion for cadaver kidneys the frequency of renal transplant artery stenosis has plummeted most likely because of endothelial cells injury) and the surgical skill.

It usually becomes apparent between 3 mo and 2 yr after renal transplantation, but it can present at any time (6). It frequently presents with worsening or refractory hypertension and/or graft dysfunction in the absence of rejection, ureteric obstruction, or infection. The salt-avid state secondary to kidney hypoperfusion and renin-angiotensin system (RAS) activation causes fluid retention. This, combined with hypertension, can cause edema, congestive heart failure, or recurrent bouts of pulmonary edema (flash pulmonary edema) that may ensue abruptly and usually resolve rapidly, particularly in patients with occlusive disease of the renal arteries (usually both). Between the bouts, patients are usually asymptomatic, the only persistent clinical sign being elevated BP.

Some patients may even have paradoxically normal or low BP, rapid deterioration of renal function, or even acute renal failure because of overzealous diuretic therapy or addition of either an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ATA II) to the antihypertensive treatment (7).

The presence of a bruit is not specific (8) because it may be caused by physiologic vascular turbulence in the iliac or femoral arteries possibly sustained by increased blood perfusion close to the anastomosis. Bruits from proximal iliac vessel
stenoses or biopsy-induced parenchymal arteriovenous fistulas can also confound the clinical picture (9). However, significant stenosis can occur in the absence of an audible bruit (10).

On the other hand, it is important to note that a bruit from iliac arteries may be as clinically relevant as a bruit from the renal arteries. Indeed, because patients at increased risk of peripheral artery disease (such as older patients and diabetic patients) undergoing a kidney transplant are progressively increasing, the possibility of an iliac artery disease that mimics TRAS (pseudo-TRAS) should always be taken into consideration. Actually, lesions proximal to the renal transplant anastomosis limit flow to the transplanted kidney with a constellation of signs and symptoms that resemble those of TRAS and may be associated with claudication or other signs of limbs hypoperfusion. These lesions may eventually be treated by interventions, including angioplasty or, more likely, surgical revascularization similar to those usually considered for TRAS (11).

In occasional cases, asymptomatic stenosis may be detected during diagnostic procedures for other clinical indications. Up to 12.4% of patients are found to have a TRAS when Doppler is done as part of routine screening in otherwise asymptomatic renal transplant recipients (compared with a prevalence of 2.4% when Doppler is used only to confirm the clinical suspicion in symptomatic patients). This provides clear evidence of the high prevalence of asymptomatic disease, as confirmed by the prevalence of TRAS: 2.4% before and 12.4% after the introduction of “screening” color Doppler (12).

**Pathogenesis**

Renal artery stenosis usually arises close to the surgical anastomosis, although pre- or post-anastomotic stenoses may also occur (10). Occasionally, the narrowing may simultaneously affect different sites along the renal artery (multiple stenoses) or the whole artery (diffuse stenoses). Different locations and timings of disease onset may reflect different etiologies. Thus, an anastomotic stenosis is most likely related to trauma to the donor or recipient vessels during harvesting, clamping, or suturing and usually arises early after transplantation (5). Small, subtle intimal flaps or subintimal dissections of the vascular wall precede intimal scarring and hyperplasia that result in narrowing or occlusion of the lumen (13). Stenoses occurring later, sometimes several years posttransplant, usually reflect atherosclerotic disease either of the transplant renal artery or of the adjacent proximal iliac artery (14).

Peripheral vascular disease is a common finding. Diffuse stenoses occurring late after transplantation may reflect immune-mediated endothelial damage. This is consistent with the finding that in this setting the histological changes, such as vascular intimal proliferation, closely resemble those of vascular rejection. However, the lack of a clear temporal association between early acute cellular rejection and subsequent stenosis challenges the hypothesis that immune-mediated damage is a primary event in the pathogenesis of late posttransplant stenosis (12,15–18). The higher incidence of stenosis in cadaver than in living-related transplants has been taken to suggest that prolonged cold ischemia may cause vascular damage and fibrosis (19). Mitogenic effects of viral cytomegalic gene products are possibly involved (20). Kinking of the artery can occur when the artery is longer than the vein and this may also simulate the hemodynamic and functional changes of TRAS (8). This may occasionally occur when the right kidney is transplanted, since it is closer to the cava vein than to the aorta and, therefore, the right renal vein is shorter than the right renal artery. When the anastomoses are completed, this discrepancy may induce a kinking of the artery that, if not recognized at the time of transplant, may require a subsequent surgical recision.

**Pathophysiology**

Renovascular hypertension is the clinical counterpart of the experimental model described as one-kidney, one-clip (1K,1C) Goldblatt’s hypertension (Figure 1), in which a clip is applied to one kidney’s artery while the contralateral kidney is removed (21), the only relevant difference being that, unlike the clipped kidney of the Goldblatt model, the transplanted kidney is denervated, and kidney hypoperfusion does not directly elicit sympathetic activation. Actually, in the early phases of 1K,1C hypertension, hypoperfusion of the single functioning kidney results in activation of the renin-angiotensin and sympathetic nervous systems, sodium retention, and extracellular volume expansion. Volume expansion and increasing BP eventually improve renal perfusion, and progressively inhibit the renin angiotensin system activity. This results in a new steady state in which hypertension is sustained mostly by extracellular volume expansion and the plasma renin activity may be normal or even low (22).

In experimental animals, kidney perfusion significantly decreases only when more than 50% of the vascular lumen is occluded (23). Angiographic studies show that in humans too renal vascular resistances (RVR) increase enough to significantly limit graft perfusion and function only when the cross-sectional area of the renal artery is reduced by more than 50% (24). When hemodynamically significant stenoses cause the kidney perfusion pressure to drop by 15 mmHg or more, rapidly progressive kidney failure and severe hypertension (10)
are common, and, without treatment, irreversible graft loss or death from cardiovascular complications (acute pulmonary edema in most cases) is the rule.

In renal artery stenosis postglomerular resistances are usually increased to sustain intracapillary pressure despite the low renal perfusion pressure (25–27). Thus, the GFR may be normal or only slightly depressed, even when kidney perfusion is severely reduced, resulting in an increased filtration fraction (FF), typical of renal artery stenosis. In experimental animals, removing the renal artery clip in time (e.g., before chronic ischemic changes occur) and restoring kidney perfusion promptly relieves postglomerular vasoconstriction (28) and is associated with a brisk increase in urine output and natriuresis, which eventually lowers arterial BP (29). The same events have been observed in humans, where restoring kidney perfusion by PTA and stenting reduced the FF, increased sodium and free water clearances, and eventually normalized BP (30). Of note in these cases, kidney perfusion was restored as soon as the diagnosis of TRAS was established. This may have some clinical relevance because a prolonged kidney ischemia may result, as in the Goldblatt model, in irreversible ischemic changes in the kidney that may prevent a full recovery of kidney function and may result in a self-perpetuating hypertension even after an effective kidney revascularization. Actually, in ischemic disease of the native kidneys, revascularization is ineffective when the resistivity index is 0.80 or higher. This increase in intraparenchymal vascular resistances reflects structural changes in the ischemic kidney that prevent functional recovery after revascularization. Although similar studies addressing this issue in transplant patients are missing so far, it can be reasonably argued that chronic changes may prevent also effective revascularization of the kidney graft and that these changes should be suspected whenever the resistivity index fails to decrease even in the presence of hemodynamically significant TRAS.

**Differential Diagnosis**

High BP and worsening renal function may be consequences of cyclosporin or tacrolimus therapy, particularly early after transplantation, when highest doses of these drugs are used. Calcineurin inhibitors can induce hemodynamic changes resembling those associated with renal artery stenosis. These drugs cause preglomerular vasoconstriction (at the site of the afferent arteriole), resulting in glomerular hypoperfusion, increased FF, sodium and water retention, and eventually increased BP (31). These changes usually recover with drug withdrawal or concomitant treatment with calcium channel blockers (32). In the long term, cyclosporin and tacrolimus also contribute to chronic vascular changes that result in chronic kidney hypoperfusion and irreversible graft damage (33).

Renal artery stenosis must also be differentiated from iliac stenoses related to atherosclerotic disease of the native recipient vessels, possibly accelerated by chronic treatment with steroids and calcineurin inhibitors (34).

Furthermore, immunologic causes of endothelial damage in TRAS have been demonstrated both in experimental and in human studies (12,15) that found histologic evidence of vascular intimal proliferation similar to the vascular intimal changes associated with chronic rejection. Chronic graft rejection, hypertension maintained by the recipients’ own contracted kidneys, or segmental infarction from incompetent or thrombosed polar arteries of the graft should also be considered in TRAS differential diagnosis.

**Diagnostic Procedures**

**Laboratory Tests.** Measuring plasma renin activity, either in basal conditions or after administration of a short-acting ACE inhibitor (ACEi), is less informative than in unilateral renal artery stenosis of native kidneys (35). As discussed before, volume expansion substantially contributes to the hypertension of posttransplant renal artery stenosis and may limit the activation of the renin angiotensin system. This might account for the relatively low plasma renin activity and falsely negative captopril tests (8). However, increased plasma renin activity is not specific for TRAS and may be the consequence of concomitant diuretic treatment or may even reflect an ongoing graft rejection (8). Serum potassium is poorly indicative too, because it may be in the normal range or even increased, particularly in patients on cyclosporin or tacrolimus therapy or with worsening renal function.

**Non-Invasive Procedures.** For years, isotope renography (basal or after renin angiotensin system stimulation) has been the most popular non-invasive screening procedure for TRAS. However, despite relatively good sensitivity (75%), the procedure is seriously limited by its poor specificity (67%) (36).

Color Doppler ultrasonography is easily accessible, relatively inexpensive, and does not require radioactive tracers (37). It has progressively replaced renal scintigraphy because of its superior performance (87 to 94% sensitivity; 86 to 100% specificity), the only limitation being that the results strongly depend on the operator’s individual experience and skill. Since identification of the renal artery is time-consuming and may be difficult in patients with multiple arteries, the operator should consult the surgery report to know whether or not multiple arteries or anastomoses problems had been present.

Correct assessment of the severity of renal artery stenosis is performed evaluating not only peak systolic velocity (PSV) at the stenotic site in the main vessel, but also resistive index (RI) in poststenotic intrarenal arteries. In fact, in suspected cases of TRAS interlobar arterial Doppler spectra should always be sampled at the upper, middle, and lower poles of the kidney and the RI should be calculated by the formula (S-D)/S, where S is the height of the systolic peak and D is the height of the end-diastolic trough.

Since PSV measurements require an angle of interrogation parallel to the vessel, which is not always obtainable by Doppler ultrasound, contrast-enhanced ultrasound does not require identification of the renal artery, nor is it angle-dependent. Furthermore, ultrasound examination during microbubble infusion can be used to quantify total organ and regional nutrient blood flow to the kidney (38).

Spiral computed tomography (CT) provides three-dimensional images of the vascular tract that may be superior to those of selective angiography, with the advantage that it does not
need artery puncture and requires less contrast medium (39). Spiral CT allows scanning of a larger volume of tissue in a shorter time than standard CT and with better peak vascular opacification after the injection of contrast medium. Moreover, regardless of patient’s age and weight, it requires the injection of no more than 120 to 150 ml of iodinated contrast material. This is important because newer non-ionic contrast media have lowered the incidence of, but have not abolished, contrast nephrotoxicity. This can be limited also with 1 ml/kg per hour 0.45% saline in the 12 h before and after the procedure, particularly in patients with impaired renal function. An obvious drawback is the high cost and limited accessibility.

Magnetic resonance (MR) angiography is even superior to spiral CT, with sensitivity ranging from 67% to 100% and specificity from 75% to 100%, but its availability is even more limited and the high costs put it out of reach of most institutions. In addition to being non-invasive, it has the additional advantage of not involving any ionizing radiation or iodinated contrast media. Actually, the contrast enhancement of MR angiography (gadolinium) is devoid of any nephrotoxicity (40).

Instrumental Invasive Procedures. Arteriography provides the definitive diagnosis of renal artery stenosis (41). The major drawback is the need for relatively large amounts of radio-contrast medium that may precipitate acute renal failure, particularly in patients with renal dysfunction (42). Thromboembolism is an even more severe complication that can cause irreversible graft function loss, and is reported in up to 9% of cases (6). Groin hematomas, pseudoaneurysms, and traumatic arteriovenous fistulas are other possible complications that, all together, occur in less than 10% of cases (43). Because of the substantial risks and the relatively high costs, renal angiography cannot be considered a screening procedure, but it is selectively indicated when a stenosis is suspected on the basis of non-invasive tests. An additional, practical feature of the procedure is that, as soon as the diagnosis is established, the stenosis can be immediately corrected by transluminal angioplasty followed by the deployment of a stent. The effectiveness of the intervention can then be immediately verified by a second angiographic evaluation.

In patients with renal insufficiency, balloon angioplasty, and stent placement can be performed using the negative contrast agent carbon dioxide, which is devoid of any nephrotoxicity (44). Stacking of optimal carbon dioxide images produces contrast columns similar to those with iodinated contrast media, giving images of the inflow iliac artery, artery anastomosis, and transplant renal artery with a resolution comparable to that of classical arteriography (45).

Treatment

Conservative Therapy. When renal function is stable and Doppler parameters (peak systolic velocity [PSV] < 180 cm/s; resistive index [RI] > 0.50) exclude hemodynamically significant stenosis (46), no specific intervention is indicated and pharmacologic treatment is usually enough to control BP. In such cases, low-dose, short-acting ACEi are effective and can be safely used if serum creatinine and serum potassium are in the normal range. Serum creatinine and potassium must be checked within 7 to 10 d after the institution of ACEi therapy. An increase in serum creatinine concentration of 30% or more versus basal should be considered as a probable marker of renal artery stenosis or decreased effective arterial volume, possibly associated with overzealous diuretic therapy, hypoalbuminemia, or decreased cardiac output. Serum potassium increase above 6 mEq/L despite optimal metabolic (in diabetic patients) and acid/base control, and concomitant therapy with thiazide or loop diuretics can be treated with potassium binding resins. In poorly compliant patients or when ACEi are poorly tolerated, dose-down titration or treatment withdrawal are indicated. Furthermore, each patient who begins ACEi treatment should be advised about possible adverse effects such as cough and laryngeal problems.

Long-term treatment with low doses of long-acting ACEi allowing single daily therapy (for instance, ramipril 1.25 mg or 2.5 mg daily, or enalapril 5 mg or 10 mg daily) can be instituted once the tolerability and efficacy of ACE inhibition have been established. This also helps protect target organs and limits cardiovascular morbidity and mortality. In these cases, regular Doppler monitoring (at least every 6 mo) is recommended for early detection of any worsening of the stenosis, even if BP is well controlled and renal function is stable.

Although there are no clear-cut data, it is reasonable that also in TRAS, as well as in renal artery stenosis of native kidneys, statins and acetylsalicylic acid should be part and parcel of the conservative treatment.

Angioplasty and Stenting. When BP can no longer be controlled, renal function progressively deteriorates, or non-invasive procedures suggest the progression of the stenosis, a diagnostic arteriography should be performed combined with angioplasty and stenting when indicated. Depending on each center’s experience and on the type of lesion, percutaneous transluminal renal angioplasty (PTA) (Figures 2 and 3) can restore kidney perfusion in 70 to 90% of cases (47). In general, the percentage of success is highest for short, linear stenoses relatively distal from the anastomosis (43), for which angioplasty and stenting are first-choice therapy. The procedure is less frequently effective and carries a higher risk of complications for stenoses at the anastomosis line (48,49). These cases are better treated by a surgical approach (6,49). With PTA alone, however, the disease may recur in 10 to 33% of cases over 6 to 8 mo (50). Recent reports, however, show that the risk of recurrence may be substantially decreased when the angioplastic procedure is combined with the placement of a stent (51). Renal artery angioplasty/stenting is best done through a retrograde ipsilateral femoral artery approach in patients with an end-to-side anastomosis and through a retrograde contralateral femoral artery puncture or a brachial artery approach when the anastomosis is to the hypogastric artery.

Once the diagnostic angiogram has been obtained and the approach that gives the best view of the stenosis established, the renal artery origin can be selectively catheterized and a guidewire advanced across the stenosis. Angioplasty balloon and stent sizing is typically obtained with the aid of computerized calibration from digital subtraction angiographic techniques imaging software (52). This combined procedure low-
ered the incidence of recurrence to less than 10% (51), an encouraging result that led some authors to suggest stent deployment already at the first angioplastic procedure. Long-term studies, however, are needed to establish the cost-effectiveness of this approach compared with repeated angioplasty (53). The risk of recurrence can be further limited by the use of radio-
active stents or stents locally releasing antiproliferative agents, such as rapamycin and enoxaparin, that inhibit intimal hyper-
plasia (54–57). Among all efforts that have been made in the prevention of arterial restenosis, drug-eluting stents must be viewed as a breakthrough and transformative technology. No solid data on their effectiveness, however, are available for the moment. A crucial point is the efficacy of the drug released by the stent. Sirolimus-eluting stents have been used in the large majority of published studies in coronary ischemia and in peripheral artery disease. Although data in coronary ischemic disease (58) are encouraging, those in peripheral artery disease (59) are to some extent disappointing. This may raise some concern about the real effectiveness of the procedure in the stenosis of the renal graft artery. Ad hoc studies are urgently needed to address this issue.

Although angioplasty with stenting is generally safe, complications occur in up to 10% of cases. Many of these are minor and relate to the puncture site. With improved equipment and the use of antispasmodics and heparin, more serious complications, such as arterial dissection, rupture, or thrombosis (60,61), occur in less than 4% of cases. In case any such emergencies should arise, a surgeon should always be on call whenever the procedure is being done.

Surgery

Surgery is indicated for patients with unsuccessful angioplasty or with very severe stenoses that are inaccessible to PTA. Surgical techniques include resection and revision of the anastomosis, saphenous vein bypass graft of the stenotic segment, patch graft, or localized endarterectomy. The success rate ranges from 63 to 92%, and the recurrence rate is close to 12% (6). In view of the high risk of complications such as graft loss (15 to 20%), ureteral injury (14%), reoperation (13%), and mortality (5%) (23), surgery is now considered as rescue therapy and should be restricted to carefully selected cases with untreatable hypertension and at high risk of major renal or cardiovascular events. Regardless of the procedure, prompt intervention is mandatory in stenosis exceeding 70%.

An important option, infrequently used, but in dramatic cases very useful, is auto-transplantation of the kidney with complex stenoses of graft arteries.

Monitoring Kidney Perfusion

No clinical parameter, including BP and serum creatinine, reliably helps monitoring kidney perfusion. Among several instrumental procedures, Doppler Ultrasound is by far the most practical and reproducible, particularly when the hemodynamic changes that accompany a significant stenosis and its effective revascularization have to be monitored serially. The procedure is highly reliable in such cases, posttreatment changes in PSV and resistive index (RI) reflecting those in renal blood velocity.
and renal vascular resistances, with 100% sensitivity and specificity (24). The reduction in RI invariably observed in hemodynamically significant and reversible stenoses may conceivably reflect peritubular and medullar hypoperfusion secondary to postglomerular vasoconstriction (62). This typically results in the so-called tardus-parvus phenomenon, where the intrarenal artery systolic upstroke is prolonged (tardus), with attenuation of the systolic peak (parvus). When the RI increases to the normal range, it invariably indicates restored kidney perfusion achieved by effective revascularization.

Furthermore, RI has an important predictive meaning also independent from TRAS presence. In fact, a renal arterial resistance index of 0.80 or higher measured at least 3 mo after transplantation is associated with both allograft failure and death with a functioning graft (63).

Conclusions
TRAS should be suspected in any renal transplant patient with severe or worsening hypertension and/or renal function deterioration unexplained by rejection or cyclosporin toxicity and occasionally precipitated by treatment with ACEi or angiotensin II antagonists. Awareness of the problem, high clinical suspicion, and liberal use of non-invasive screening/diagnostic procedures (e.g., Doppler ultrasonography) may help detecting virtually all hemodynamically significant stenoses. The importance of early diagnosis is self-evident because unrecognized cases invariably result in graft loss and potentially fatal systemic complications, whereas cases promptly recognized and treated before irreversible structural changes of the graft develop may achieve full recovery of kidney perfusion and function with minimal risks (Figure 4). Whether and to what extent this improves long-term graft survival needs investigation in properly designed and powered longitudinal studies.

References

Figure 4. Algorithm of posttransplant renal artery stenosis management.

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